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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,827	01/31/2005	Simona Jevsevar	LB/G-32992A/LEK	2050

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER
XIE, XIAOZHEN

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,827	JEVSEVAR ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-22 and 24* is/are pending in the application.

4a) Of the above claim(s) *24* is/are withdrawn from consideration.

5)☐ Claim(s) *6,8,9,11,13 and 14* is/are allowed.

6)☒ Claim(s) *2-5, 7 and 15-22* is/are rejected.

7)☐ Claim(s) *1 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 January 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050131*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statement (IDS) submitted 31 January 2005 is acknowledged. Applicant's amendment of the specification filed 31 January 2005 has been entered.

Election/Restrictions

Applicant's election of Group I in the response received 6 July 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 12 and 23 are cancelled. Claims 1-11, 13-22 and 24 are pending. Claim 24 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 1-11 and 13-22 are under examination.

Information Disclosure Statement

The information disclosure statement filed 31 January 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Sequence Rules Compliance

The Instant application is not fully in compliance with the sequence rules, 37 CFR 1.821-1.825 for the following reasons: the sequences in Figure 2 and in the specification do not have sequence identifiers. See MPEP§2421.02(d).

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Appropriate correction is required.

Claim Objections

Claims 1, 3, 5, 10, 11 and 15-20 are objected to because of the following informalities:

Claims 1 and 11 recite "SEQ ID: 1" which should be "SEQ ID NO: 1.

Claim 3 should delete "for" to be grammatically correct.

Claim 5 recites "which <u>are</u> not changed…". "Are" should be "is".

Claim 10 recites "the plasmid vector comprises a resistance gene selected from the group consisting of ampicilline and a kanamycine". Ampicillin and kanamycin are antibiotics, not resistance genes. It should be "the plasmid vector comprises a resistance gene selected from the group consisting of an ampicillin resistance gene and a kanamycin resistance gene". Also, there is a typographical error for kanamycin (not kanamycine).

Claim 11, line 1 should be "<u>a</u> DNA sequence", and line 4 should be "a production strain <u>of</u> *E. coli*".

Claim 15, line 1 should be "a DNA sequence". Also, claim 15 is awkward in reciting "maintaining a completely unchanged part".

Claim 16, line 1 should be "a DNA sequence", and line 2 should be "the 5'-untranslated region".

Claims 17-19 should be "a DNA sequence".

Claim 20 is grammatically incorrect in reciting "the DNA sequence according to the expression plasmid according to claim 6 in *E. coli*".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 4 and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite for referring nucleotide positions (e.g., positions 3 and 194, positions 194 and 309, positions 309 and 467, and positions 467 and 536) without referring a SEQ ID. The native hG-CSF nucleic acid sequence can have varying lengths, e.g., different lengths in the 5' or 3' terminus. Therefore, the nucleotide positions would vary.

Claim 2 is unclear and indefinite for reciting "the sequence comprises a nucleotide sequence selected from the group consisting of a combination of the following modifications with respect to the native hG-CSF sequence". A nucleotide

sequence cannot be selected from a list of modifications. Further, "A combination of modifications" does not imply that all the modifications need to be present, e.g., a combination of two modifications.

Claim 2, line 10, is unclear and indefinite for reciting "essentially no change".

Claim 2, lines 4, 7, 9 and 11, is unclear and indefinite for reciteing "in a "segment I"….". Are there more than one "segment I"? It appears that "a" should be deleted.

Claims 4 and 19 are indefinite for the recitation of "an expression level of G-CSF, to the total proteins after expression, of at least 50%". It is unclear what quantization method the claim is intended to mean. For example, does the percentage refer to dry weight, or scanning Coomassie blue stained SDS-PAGE gels of whole lysates?

Claim 15 is indefinite for the recitation of "applying methods". It is unclear what methods need to be applied.

Claim 15 is indefinite for the recitation of "a substantial portion". The specification does not have definition for such portion, and the metes and bounds cannot be determined.

Claim 16 is unclear and indefinite for reciting "partial regions". Which part of the regions are encompassed?

Claims 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The instant claims are drawn to a process for construction of DNA sequence according to claim 1. However, there are no steps set forth that delineate the method. There is an absence of a resolution step which reads

back on the preamble of the claimed method. Without a resolution step, it is unclear which codons or regions need to be changed, and what DNA sequence is constructed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-4, 7, 15, 17, 19, 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Hockney et al. (U.S. Patent No: 5,840,543, issued on 24 November 1998).

The claims are directed to a DNA sequence, an expression plasmid, and a process for construction of the DNA sequence, characterized in that the sequence comprises a nucleotide sequence selected from the group consisting of a combination of the modifications with respect to the native hG-CSF sequence: a plurality of replacements of *E. coli* rare codons with *E. coli* preference codons in segments I, II, IV; replacements of GC rich regions by AT rich regions in segment I; no change or essentially no change in segment III (claims 2, 7, 15, 17); wherein the DNA sequence encodes for a biologically active G-CSF (claim 3), and is capable of providing an expression level of G-CSF to the total protein after expression, of at least 50% in an expression system (claim 4, 19); wherein the expression is in *E. coli* (claim 20).

The '543 patent teaches hG-CSF variant polynucleotides, and plasmids comprising same, bearing silent substitutions (codon optimization) for improved expression levels. The '543 patent teaches that the silent substitutions are distributed over the entire hG-CSF sequence (i.e., in the 4 different segments as recited in the instant invention). Many of the substitutions are identical to those as described on pages 9-10 of the instant application (see Figure 6 and 7 of the '543 patent, and comparing the sequence with Fig. 2 of the instant invention). The '543 patent further teaches preparation of the DNA construct and expression of the construct in an *E. coli* fermentation process (column 7, line 26 through column column16, line 8, and in Examples 1-5). The fact that Applicant further limits through dependent claims 4 and 19, by reciting a specific yield of G-CSF (i.e., an expression level of G-CSF to the total protein after expression, of at least 50%) does not render the claims patentable. These are merely inherent characteristics of the product and process taught by the '543 patent, since the product and the process are identical between the prior art and the instant invention. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Therefore, The '543 patent anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 16, 18, 21, 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hockney et al. (U.S. Patent No: 5,840,543), in view of Baneyx et al. (Curr. Opin. Biotech., 1999, 10:411-421).

The '543 patent teaches as set forth above. The '543 patent, however, does not teach adding an unchanged 5'-UTR, or unchanged partial regions of the 5'-UTR (including translation initiation region, ribosome binding site, and the region between the start codon and the ribosome binding site) to the hG-CSF gene (claim 5, 16); Nor teaches that the plasmid comprises a T7 promoter sequence (claim 18); and that the expression is induced with IPTG (at least 0.1 mM to less than 1 mM), and fermented at a temperature of about 20°C to 30°C (claims 21, 22).

Baneyx et al. teaches expression of recombinant proteins in *E. coli*. Baneyx et al. teach that mRNA transcripts in *E.coli* are rather unstable, and that the inclusion of 5' UTR can increase mRNA stability (page 414, left column). Baneyx et al. teach that the pET vectors, in which target genes are positioned downstream of T7 promoter, have gained increasing popularity (pp. 412, column 2, 3rd paragraph). Baneyx et al. teach that IPTG, as little as 50-100 μM, is sufficient for induction of recombinant protein expression in *E. coli* (page 412, right column, 1st paragraph). Baneyx et al. teach that low temperature cultivation conditions in the T7 expression system favor proper protein folding (page 413, left column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the '543 patent to include the 5'UTR into the

DNA construct, and using the T7 expression system (i.e., T7 promoter, IPTG induction, and lower cultivation temperature). One of ordinary skill in the art would have been motivated to do so, because the '543 patent teaches a DNA construct and an expression system that improves G-CSF expression in *E. coli*, and Baneyx et al. teaches elements that can increase mRNA stability and protein folding. Therefore, the combined teachings provide a reasonable expectation of successfully expressing hG-CSF in *E. coli*.

Conclusion

CLAIMS 6, 8, 9, 13 AND 14 ARE ALLOWABLE.

CLAIMS 1, 3, 5, 10, 11 AND 15-20 ARE OBJECTED.

CLAIMS 2-5, 7 AND 15-22 ARE REJECTED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
September 10, 2007

Eileen B. O'Hara

EILEEN B. O'HARA
PRIMARY EXAMINER